## REMARKS

Applicants respectfully request entry of the amendment and reconsideration of the claims. Claims 19, 38, and 61 have been amended. The amendments are supported throughout the specification including at page 53, lines 29-33, page 54, line 31 to page 55, line 2, page 55, lines 13-22, and Examples 3 and 4.

Claim 67 has been canceled without prejudice or disclaimer. Applicants reserve the right to pursue the subject matter of this claim in a continuation application.

**Enablement**

Claims 19, 38, 42-48, 51-57, 61-64, and 66-75 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

The Office Action alleges the specification fails to teach how to use the claimed methods for detecting cancer in pancreas, liver, colon, thyroid, kidney, or bladder. The Examiner alleges the tumor marker data provided in the specification does not enable the full scope of the claims. According to the Office Action, it is unclear if the nucleic acid levels are enhanced or decreased compared to normal control tissues because of inconsistent expression of the nucleic acid molecules in the same tissues. Applicants respectfully do not agree.

To meet the enablement requirement of 35 U.S.C. §112, first paragraph, a specification must contain a sufficient description to enable one skilled in the art to make and use the claimed invention (*See, e.g., Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1253 (Fed. Cir. 2004); MPEP §2164.01). A specification does not need to explicitly disclose every detail, and may omit what is well known in the art (*In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); MPEP 2164.01). To make and use an invention may require experimentation even if the specification is enabling (*In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988); *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984); MPEP §2164.01). The experimentation must not be unduly extensive (*Id.*), however, costly and timely experimentation alone does not constitute undue experimentation. (*U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988)).

Applicants submit that the Examiner is requiring Applicants to establish enablement to a higher degree of certainty than is required. An enabling disclosure only requires a reasonable correlation to the scope of the claims, absolute certainty is not required. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement is satisfied (*In re Fischer*, 427 F.2d 833, 839 (CCPA 1970)). For a claimed genus, representative examples coupled with a statement applicable to the genus as a whole are ordinarily sufficient to comply with the enablement requirement (MPEP § 2164.02).

Without acquiescing to the rejection and solely for the purpose of advancing prosecution, the claims have been amended to recite detecting an increase in expression of the nucleic acid molecules in a tumor cell or cancer cell compared to a normal cell, wherein the tumor cell or cancer cell is a pancreas, liver, colon, thyroid, or bladder cell. Support for the amendment can be found in the specification, for example, at page 53, lines 29-33, page 54, line 31 to page 55, line 2, page 55, lines 13-22, and Examples 3 and 4.

When the breadth of the claims, nature of the invention, the state of the prior art, level of skill in the art, level of predictability, amount of direction, existence of working examples, and the quantity of experimentation are considered, Applicants submit that the specification as filed enables the claimed subject matter. Applicants submit the claims are directed to a method for determining the presence of cancer in a subject comprising:determining a level of expression of a polynucleotide of SEQ ID NO: 5 or a nucleic acid encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:3 or SEQ ID NO: 6 in a tissue sample from the subject, wherein the tissue sample comprises pancreas, liver, colon, thyroid, or bladder cells. The claims include reference to the nucleic acid and amino acid sequences and reference to certain types of cancer cells. The level of skill in the art is high, and working examples are provided. The specification provides direction to those of skill in the art by providing the sequences, the structures, and the function of the polypeptides as well as working example showing detection of nucleic acids encoding the polypeptides in tumor tissue.

Applicants submit that they have described the sequences. See the specification at pages 7-8 . Applicants have described that the S100/CaBP type calcium proteins have been associated with cancer, for example, malignant melanoma, and astrocytic tumors. See the specification at

page 11, line 29 to page 12, line 24. The mouse sequence disclosed in the application was identified as differentially expressed in mouse mammary tumors that arise spontaneously in Wnt-1 transgenic mice. The human sequence includes an est sequence that originated from a human cell that forms metastatic tumor when implanted in mice. See the specification at page 10, lines 8-21. Applicants have provided working examples detecting an increase of the determining a level of expression of a polynucleotide of SEQ ID NO: 5 or a nucleic acid encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:3 or SEQ ID NO: 6 in a tissue sample from the subject. Table 8 shows an increase in expression of the nucleic acid molecules in pancreas, liver, colon, stomach, thyroid, and bladder cancer cells relative to normal cells from the respective tissues. Table 9 shows expression of the nucleic acid molecules in tumor tissue compared to normal adjacent tissue in the same patient or normal tissue from a different patient. Expression of the nucleic acid molecules in colon, liver, stomach, thyroid, and bladder, for example, is generally increased in Table 9 relative to the control.

Applicants submit the data provide in Tables 8 and 9 provide a reasonable correlation between an increase in expression of the nucleic acid molecules in the recited cells and tissues and cancer. Contrary to the Examiner's assertion, Tables 8 and 9 provide a control cell or control tissue for each cell type or tissue type. For example, many of the malignant tissues in Table 9 are accompanied by matched margins taken from normal tissue(NAT) surrounding the zone of surgery.

The Office Action alleges one of skill in the art would not be able to practice the claims because the data in Tables 8 and 9 with respect to expression of SEQ ID NO:5 in kidney and colon is inconsistent with the summary of the data at pages 88, lines 1-10 and page 91, lines 1-8. Applicants respectfully do not agree.

Without acquiescing to the rejection and solely for the purposed of advancing prosecution, the claims have been amended to recite detecting an increase in expression of the nucleic acid molecules in a tumor cell or cancer cell compared to a normal cell, wherein the tumor cell or cancer cell is a pancreas, liver, colon, thyroid, or bladder cell. Applicants reserve the right to pursue the canceled subject matter in a continuation application.

A summary of the data in Tables 8 and 9 related to expression of SEQ ID NO:5 in colon is provided below in Table A. The data has been reorganized to show a comparison of tumor tissue with normal tissue.

Table A

| Table | Tissue | Identifier | Normal (Rel. Expr. (%)) | Cancer (Rel. Expr. (%)) |
|---|---|---|---|---|
| 8 | Colorectal | | 3.6 | |
| | Colon | SW480 | | 0.3 |
| | Colon | HT29 | | 12 |
| | Colon | CaCo-2 | | 44.2 |
| | Colon | OD03866 | | 9.8 |
| | Colon | HCC-2998 | | 100 |
| | Colon | NCI-N87 | | 37.8 |
| 9 | | | NAT(matched) | Tumor |
| | Colon | OD03866 | 11.5 | 32 |
| | Colon | OD03868 | 2.7 | 19.1 |
| | Colon | OD03920 | 5.2 | 5.7 |
| | Colon | OD03921 | 10.8 | 6.9 |

Table 8 shows expression of SEQ ID NO:5 in tumor cells compared to normal cells of the same tissue type. Lines 1-8 at page 88 discloses that "[t]he results in Table 8 indicate that the clone of SEQ ID NO:5 is very strongly expressed in several tumor derived cells lines compared with normal tissues, especially colon tumor cells, breast tumor cells and ovarian tumor cells" (emphasis added). Five out of the six colon tumor cell lines tested in Table 8 exhibited greater expression of SEQ ID NO:5 compared to the control colorectal sample (see Table A above).

Table 9 shows expression shows expression of clone 65677221-3-frag in tumor samples and "matched margin" normal tissue (NAT, *e.g.*, normal tissue surrounding the zone of surgery). These results show an increase in expression in tumor tissue as compared to tissue from the margin surrounding the tumor. The variability in the data could reflect variation seen in actual tumor tissue or the fact that the normal associated tissue may also contain some cells that are cancerous or precancerous. The summary of the data beginning at line 2 on page 91 states that "[t]he results shown in Table 9 demonstrates that clone 65677221-3-frag is strongly upregulated by cancer cell lines and tumor, compared to normal tissue and normal adjacent tissue. This is especially true for cancers of breast, ovary, colon, stomach, and pancreas."

Applicants' claims are directed to detecting expression of a nucleic acid sequence in pancreas, liver, colon, thyroid, or bladder cells. Applicants submit that, in the least, the data supports the relationship between upregulation of the nucleic acid sequence and the claimed tumor cells. Applicants further submit that any experimentation that might be necessary could be readily conducted by one of skill in the art following the examples in the specification, and would be routine.

In addition, Applicants' teaching that an increase in expression of SEQ ID NO:5 in colon cells or tissue is a useful marker for colon cancer is confirmed by the post-filing reference of Smirnov et al., 2006, *Cancer Res.*, 65:4993 (analysis of circulating tumor cells indicates that S100A 14 serves as a marker for breast cancer and colon cancer cells). This post filing date reference was submitted as evidence that confirms Applicants results as described and exemplified in the specification.

In view of the guidance and working examples provided in the specification and discussed herein, one of skill in the art would reasonably conclude that the summary of the data at lines 1-8 on page 88 and lines 2-4 on page 91 is not inconsistent with the colon expression data shown in Table 8 or Table 9. Tables 8 and 9 (as illustrated more clearly in Table A above) reasonably establish that an increase in expression of SEQ ID NO:5 in colon cells correlates with cancer.

In view of the forgoing, Applicants submit the specification provides sufficient guidance and working examples such that the claims as amended could be practiced without undue experimentation. Withdrawal of the enablement rejection is respectfully requested.

**New Matter**

Claims 19 and 42-48 were rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. This is a new matter rejection. Applicants respectfully traverse this rejection.

Claim 19 has been amended to recite "detecting an amount of said nucleic acid molecule in said sample, wherein an increase in expression of the nucleic acid molecule as compared to normal cells of the same tissue type is indicative of cancer". Applicants submit the amendment

is supported by the specification for the reasons discussed below and therefore does not constitute new matter.

The written description requirement does not require *ipsis verbis* or *in haec verba* support in the specification for newly added claim limitations. MPEP §§ 2163(I)(B), (II)(A)(3)(a), and (II)(A)(3)(b). In order to comply with the written description requirement, each element of the claim must be expressly, implicitly, or inherently supported in the originally filed disclosure. MPEP §§ 2163(I)(B) and (II)(A)(3)(b).

Moreover, the written description requirement must be applied in the context of the particular invention and state of the knowledge. *Capon v. Eschar*, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005). It is unnecessary to spell out every detail of the invention in the specification. Only enough must be included to convince a person of skill in the art that the inventor possessed the invention. *Falkner v. Inglis*, No. 05-1234, slip. op. at 14 (Fed Cir. May 26, 2006) (citing *LizardTech, Inc. v. Earth Resource Mapping, PTY, Inc.*, 424 F.3d 1336, 1345 Fed. Cir. 2005). If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. MPEP § 2163(II)(A)(3)(a) citing *Vas-Cath v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991) and *Martin v. Johnson*, 454 F.2d 746, 751 (CCPA 1972) (emphasis added).

Applying these standards, Applicants submit claim 19 as amended is adequately supported by the specification and does not constitute new matter. For example, the specification at page 53, lines 29-33 and page 54, line 31 to page 55, line 2 describes a diagnostic assay comprising detecting expression of a FCTRX nucleic acid in a biological sample and a control sample and comparing expression of the nucleic acid in the biological sample with expression of the nucleic acid in the control sample. Page 55, lines 13-22 discloses that the diagnostic assays can be used to detect a disease or disorder associated with aberrant FTCRX expression, such as cancer. Working examples 3 and 4 and Tables 8 and 9 show that expression of a FCTRX nucleic acid, such as SEQ ID NO:5 or clone 65677221-3-frag, is generally increased in pancreas, liver, colon, thyroid, and bladder cancer cells or cancerous tissue relative to expression of the nucleic acid in normal cells or tissue. The data in Tables 8 and 9 clearly

demonstrate that detecting an increase in expression of the FCTRX nucleic acid in pancreas, liver, colon, thyroid, or bladder cells or tissue is useful for detecting cancer in said cells or tissue.

In view of the forgoing, Applicants submit claim 19 as amended is adequately supported by the specification and does not constitute new matter. One of skill in the art would have understood Applicants to be in possession of the claimed subject matter. Withdrawal of the written description rejection is respectfully requested.

**Conclusion**

In view of the above amendments and remarks, Applicants submit the claims are in condition for allowance and respectfully request a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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